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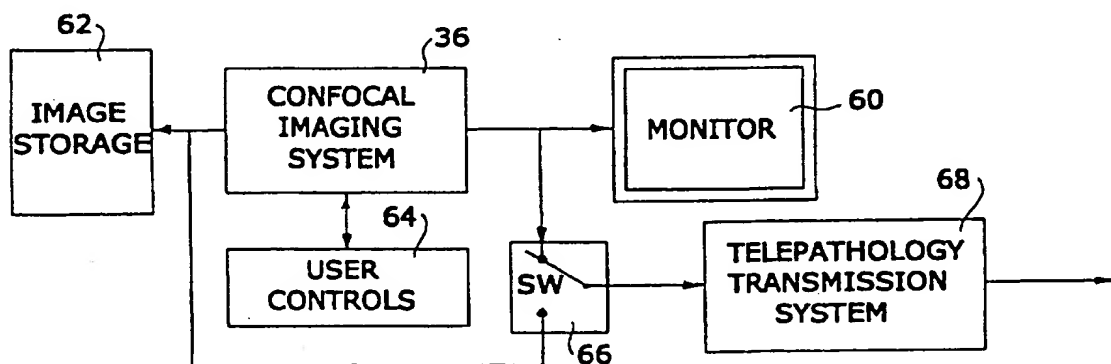
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(54) Title: TISSUE SPECIMEN HOLDER



(57) Abstract

A tray or holder (10) for tissue specimens (34), especially of excised tissue, such as biopsied specimens, is used with a confocal imaging system (36), especially a laser scanning confocal microscope system. The tray may be disposable after imaging of the specimen carried therein or may archive the specimen. A window (32) supports the specimen. Clamps (40) mounted inside the tray restrain the tissue. A compliant bag (44) is mounted outside the tray on one side of a window (34) of the tray on which the specimen is disposed. During imaging the specimen is immersed in a liquid (38) contained in the tray having an index of refraction which closely matches the index of refraction of the tissue. The bag also contains an index matching liquid (39) preferably having the same index of refraction.

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TISSUE SPECIMEN HOLDER

Description

The present invention relates to a tissue specimen holder or tray for use in microscopy and particularly in laser scanning confocal microscopy for imaging sections of surgically excised specimens. The invention is especially suitable for providing a tissue tray which aids in the imaging of a wide variety of tissue samples which may be excised tissues or biopsies of various tissues, such as liver, kidney, cervix, et cetera.

It has been proposed to provide for the imaging of specimens in an immersion liquid which matches the index of refraction of the tissue (See U.S. Patent 5,719,700, issued Feb. 17, 1998 to P. Corcuff, et al and U.S. Patent 4,208,101, issued June 17, 1980 to L. Trapp, et al). Handling of the tissue specimens and the immersion liquid is difficult. The specimens are small and the liquid can run over a slide on which the specimen is mounted. In short, handling and preparation of specimens for imaging is, with the proposed systems, a messy operation. In addition, variations in optical path between the section of the specimen of interest and the imaging system can distort the image. Such distortions are exacerbated by the corrugated surface provided at the surface of the specimen. For high fidelity imaging, the immersion fluid must closely match the tissue index. Matching the refractive index of the immersion fluid to the tissue greatly reduces the optical refracting power of tissue and therefore the optical path difference introduced by the tissue.

It is a feature of the invention to provide specimen holders or tissue trays optimized for different tissues which are usable with the same imaging system, and without replacement or adjustment of objective lenses. The tray provided by the invention may be used to contain the specimen for short term or long term storage or to transport the tissue for additional processing. The tray may be disposable after use. The tray contains and also has associated therewith index matching liquids. The tray facilitates the use of such liquids without messy operations and without adversely affecting imaging (imparting distortion to the image because of the presence of the index matching liquids).

The confocal laser scanning microscope imaging systems having objective lenses which are capable of forming images of different sections having different orientations within a specimen may be of the type described in allowed U.S. Patent application serial number 08/683,607 filed July 15, 1996 in the name of R. Rox Anderson et al., now U.S. Patent No.

5,880,880, issued March 9, 1999, and U.S. Patent 5,788,639, filed in the names of James Zavislan and Jay Eastman and issued August 4, 1998.

Briefly described, a specimen holder in accordance with the invention includes a container having a window through which an optical beam passes into a specimen disposed in the container over the window. The container may be in the form of a specimen tray. The specimen is preferably held in place by clamps which may be automatically applied when a cover of the container is closed. In use, the container includes an immersion liquid which closely matches the index of the tissue. Matching may be to the average index at the surface of the tissue which interfaces with the window. The tissue surface may be corrugated due to natural or surgically produced surface texture. Such corrugation may alter the wavefront of the beam (make the wavefront depart from a section of a sphere) which enters the tissue and is focused in the tissue section of interest. The distortion due to such variations is reduced in accordance with the invention by virtue of minimizing the variation of optical path lengths, notwithstanding that the section at which the beam is focused may be at the surface of the tissue or within the tissue (for example a distance of up to approximately 3mm from the surface) by use of immersion liquids and coupling liquids and other transmissive elements, including the window, through which the imaging beam passes. The coupling medium is contained in a bag outside the container and facing the window. The bag is made of compliant transmissive material such as a polymer, for example polyethylene, but is of a minimum thickness so as not to have any material effect on the optical path through the bag. The bag contains a liquid coupling medium. Mounted on the bag is a stabilizing plate of transmissive material. The plate is opposed to the window, and preferably contains a lock-in unit such as a magnet or magnetic ring which is received in a notch at the top of a barrel containing the objective lens of the imaging system. The objective lens and the tray is supported on a fixture which is mounted on a common structure with the objective lens via a translation mechanism, which moves the fixture and the container in nominally orthogonal directions, one of which is along the optical axis of the lens. The index of the coupling medium is preferably the same as the index of the immersion liquid. The tray may have a passageway which is pierced by a protrusion on the cover of the tray so as to allow the coupling liquid to fill the tray and provide the immersion liquid. The stabilizing coupling of the plate to the objective lens prevents tilting and maintains the plate perpendicular to the optical axis notwithstanding of motion of the container so as to bring sections of the specimen

of interest into focus and to scan the specimen in the plane of the section. In order to minimize optical distortion, due to changes in optical path between the exit pupil of the objective lens and the section of the specimen being imaged, in spite of the corrugations caused by the surface, the difference between the index of refraction of the immersion liquid and the average index of refraction of the tissue at its surface, multiplied by the height between the peaks of the hills and bottoms of the valleys of the corrugations, is selected to be equal or less than a quarter wavelength at the wavelength of the laser beam used for imaging. Since the average index is a function of tissue type and clinical condition of the patient, the index matching fluids can be selected in the preparation of the tray for the particular tissue to be imaged. In addition, the thickness and index of the window and the plate may be varied depending upon the type of tissue in the tray in order to reduce spherical aberration for the objective lens used in the imaging system.

The foregoing and other features and advantages of the invention will become more apparent from a reading of the following description taken in connection with the accompanying drawings in which:

FIG. 1 is a diagram schematically showing the imaging system, its objective lens and a container providing a tray with the tray in one of two alternative positions, where the section is near the surface of the tissue sample, FIG. 1B shows the position where the section is within the tissue sample (specimen);

FIG. 1A is an enlarged view of the section shown within the dashed lines labeled 1A-1A in FIG. 1;

FIG. 1B shows the objective lens and tray where the beam is focused at an image plane within the specimen, where the section being imaged is located;

FIG. 2 is a diagram illustrating the fixturing for the tray and the mechanism for adjusting the position of the tray in three orthogonal directions, X, Y, and Z;

FIG. 3 is a diagram showing the tray in process of preparation;

FIG. 4 is an enlarged view illustrating one of the clamp mechanisms used in the tray;

FIG. 5 is a diagram illustrating the tray where the cover is in process of being closed;

FIG. 6 is a view similar to FIG. 5 showing the tray after closure of the tray;

FIG. 7 is a sectional top view taken along the line 7-7 in FIG. 6;

FIG. 8 is an enlarged view schematically illustrating the corrugations formed by surface texture at the surface of the tray.

Referring more particularly to FIGS. 1, 1A, 1B, 2 and 7, there is shown a tissue holder or tray 10 mounted on a support platform 12. The support platform 12 is moveable by a translation mechanism 14 which is mounted on a stand 16 which holds an objective lens assembly 18 in a nominally fixed position. The platform 12, translation mechanism 14 and stand 16 provide a tray support fixture which can receive various trays. The lens assembly 18 includes a lens barrel 20 and a lens 22 mounted within the barrel. The upper end of the barrel has an annular notch 24 in which a portion of the tray 10 is received and locked, as will be discussed in greater detail below.

The tissue tray or holder 10 is an assembly having a generally open specimen container or box with a plate providing a base 26, sidewalls 28 and a cover 30, which may be hinged to one of the side walls. The shape of the box is shown as rectangular but it may be circular or oblong. The base has an opening containing a window 32 of transparent material. The thickness and refractive index of this window is selected to accommodate the design of the lens 18 and the index of refraction of the tissue specimen 34. The specimen may be surgically excised.

A compliant bag 44 of thin, optically transparent material, is attached to the underside of the base 26 of the tray 10. This bag is initially filled with an optical coupling medium which may also provides an immersion medium for the specimen 34. To prepare the tray, the specimen 34 is placed on the window 32 as shown in FIG. 3. Clamping mechanisms 40 are then used to hold down the tissue specimen on the window for viewing, as shown in FIG. 5. The mechanisms are shown engaging the specimen 34 in FIG. 5, but may automatically engage the specimen when the cover is closed, as shown in connection with FIG. 4. When the cover is closed, a pin 50, carried on the cover, pierces a plug 45 in an opening 46 which provides a passageway for the flow of the coupling medium into the tray through the pierced opening 46. When the tray 10 is placed on the support platform, a transparent stabilizing plate 52 which is attached to the bag 44 in a location near the bottom of the bag opposite to the window 32, is captured in the notch 24 at the upper end of the lens barrel. The relative heights of the platform 12 and the lens barrel 24, both of which are supported in the fixture 16, is such that the bag 44 is compressed by the lens barrel and the shape thereof changes from the shape shown in FIG. 5 to the shape shown in FIG. 6. Then the liquid optical coupling medium 39 flows through the hole 46 and encompasses the specimen. The coupling liquid then serves as the immersion liquid. In another embodiment of the invention, the tray

may be filled with the immersion liquid, and, when the plug is pierced, the immersion liquid flows into the bag. In a further embodiment, the bag and tray are independently filled. When plug 45 is opened the fluids can mix. In a further embodiment the bag and tray are independently filled. There is no plug 45 and the liquids remain separate.

In either case, the height of the liquid above the lens and above the base depends upon the relative position of the tray and may vary as the tray is moved to select the focus in the section of the specimen to be imaged. See FIG. 1B. The configuration of the bag also changes as the tray moves with respect to the objective lens 18 to scan the section.

The objective lens 18 may be a generic lens which is corrected for spherical aberrations for a cover slip of certain index N_T and thickness T . The spherical aberration present in the objective lens is equal and opposite the spherical aberration introduced by the cover media or slip. When the focus is adjusted to the top surface of window 32, the cover medium includes plate 52, coupling medium 39, and window 32. The spherical aberration can be described by several representations such as longitudinal ray aberration, transverse ray aberrations or wavefront aberration. Using the longitudinal ray aberration, the spherical aberration = LA_T . The longitudinal aberration can be minimized by a single plate of index N_T and thickness T or a series of plates such that where the plate is in air,

$$LA_T(N_T, T) = \sum_{i=1}^{i=N} LA_T(N_i, t_i),$$

$$\text{where, } LA(N_i, t_i) = \frac{t_i}{N_i} \left[1 - \frac{N_i \cos U}{\sqrt{N_i^2 - \sin^2 U}} \right]$$

and where U is the angle in air with respect to the optical axis of the marginal ray in the converging beam. N_i and t_i is the index and thickness of each of the plates. The relationships when the plate is liquid are similar. See Warren Smith, Optical Engineering, pages 96-99 published by McGraw Hill, (1990) for further information on the equations given above.

Aberration is introduced by the specimen and particularly by the surface texture of the specimen in the optical path (along the axis of the lens 18). A laser beam from a confocal imaging system 36 passes through the lens along the optical path and is focused in the specimen. The tissue defines a corrugated surface as shown in FIG. 8. There is index variation between the tissue surface and the window 32, which may be accommodated in part,

by a selection of the index and thickness in the direction of the beam (along the optical axis) through the window 32. The other indices of refraction of the elements in the beam path are also taken into account in determining the thickness and index of either the window 32, plate 52, or both. The primary determinative of the index and thickness of the window 32 is the index of the tissue of the specimen 34. Thus, the index and thickness of the window 32 (or plate 52) will depend upon the type of specimen being imaged. Different trays 10 are provided for different types of specimens (kidney, liver, cervix, et cetera) and each will have a somewhat different window thickness and index in order to reduce spherical aberration.

An immersion liquid 38 having an index which generally matches the average index of the tissue of the specimen 34 is contained in the tray. This liquid may serve also as a tissue preservative or fixative.

When the tissue specimen 34 is placed in the tray in the base 26 and over the window 32 as shown in FIGS. 3 and 4, the specimen 34 is held down by the clamp mechanism 40. The clamp mechanism which is illustrated has hooked or barbed fingers which are hinged to the sidewalls 28 at spaced locations. The mechanisms include springs 42 which provide over center locks, such that when the fingers are pressed down beyond their axis of rotation, they are held down by the springs 42. Other clamping mechanisms may be used such as meshes or a membrane overlay or a permeable or perforated bag. Fiducial marks, which can be visualized or imaged, may be provided in the case of meshes or membranes. The use of a membrane or mesh may be preferable since the specimen 34 may be moved under the membrane. The membrane specimen tray or cassette is the subject matter of a companion application filed concurrently herewith in the name of Bill Fox, et al. Further information as to the use of the markings on the clamping mechanism (the mesh or membrane) to mark locations of the image tissue is contained in a co-pending International Patent Application No. PCT/US99/21116, and U.S. Patent Application, filed in the names of Roger J. Greenwald and James M. Zavislan, serial number 60/100,176, filed September 14, 1998. The purpose of the clamps is to keep the tissue stationary during examination and also provide a means to lightly compress the tissue surface against the window. Alternatively, the clamps may provide tension to pull the tissue surface taut. Holding the tissue with either compression normal to the window or in tension parallel to the window (or both) tends to reduce the surface texture, or corrugation, peak to valley depth.

As shown in FIG. 1, the thin compliant bag 44 is attached to the base 26 and encompasses the window 32 and the initially plugged opening 46. The bag is filled with the optical coupling medium 39, which may have an index selected in order to reduce image distortion due to the corrugations formed by the texture surface of the specimen 34 via which the optical imaging beam passes. Preferably the coupling liquid is the same as the immersion liquid 38 and the coupling liquid may flow through the opening 46 which may initially have a plug 45 and be plugged and then opened by the pin 50 carried by the cover 30, when the cover is closed as shown in FIG. 6.

The stabilizing plate 52 is attached to the bag 44 opposite to the window 32. This plate has an index of refraction and thickness which is taken into account in selecting the thickness and index of the window 32. A magnet or magnetic ring 56 surrounds the plate 52. See FIG. 1A. The plate 52 may be held by fusing, welding, cementing, friction or screw fit into the ring 56. The ring is permanently attached, as by a fused or cemented connection, to the bag 44, or to an opening in the bag. The diameter of the ring 52 is sized to fit into a notch 58 at the upper end of the barrel of the objective lens. The barrel may be made of magnetic material so as to lock the bag 44 in place on the assembly of the objective lens 18. The attachment is removable since the hold down force is magnetic. Other removable or releasable lock in mechanisms, such as snaps, may be used. The plate 52 may be curved or of a meniscus shape to provide optical power added to the power of the objective, if desired.

The confocal imaging system 36 may be of the type described in the above referenced Anderson and Zavislan patents. Imaging systems using two-photon microscopy or optical coherence tomography may also be used. See Denk et al., U.S. Pat. No. 5,034,613 and Schmitt et al., Proc. SPIE, volume 1889 (1993). Associated with the imaging system is a monitor or display 60 which provides a display of the image of the section. The image may also be stored digitally in memory shown as image storage 62. The location of the section being imaged is obtained by user controls 64 which may provide signals for actuating drive motors or other actuators in the translation mechanism 14 which selects the section to be imaged and can scan the section. Alternatively, the translator stage may be manually controlled by the use of micrometers. The image storage 62 or the imaging system may be connected through a switch 66 to a telepathology transmission system 68 which transmits the image to a remote location. Such a system 68 is the subject of U.S. Patent 5,836,877 issued November 17, 1988 to J. Zavislan.

As shown in Figs. 1 and 1B, the lens 18 may focus the beam at the surface or within the specimen by moving the support 12 thereby varying the distance between the lens and the tray. As the distance along the optical axis to that inside the tissue changes, the thickness along that axis of the coupling and medium 39 varies in an opposite sense. This keeps the optical path constant, even though the section may be well within the specimen. This inverse relationship of bag thickness to focus depth is in a direction to compensate for aberration due to physical length variations between the lens and the section of the medium being imaged.

As shown in FIG. 8, the corrugations due to the surface texture of the specimen 34 creates corrugations having a depth (h) (from the apex of the corrugation peaks to the bottom of the valleys of the corrugations) which may be approximately 200 microns in length. The index of refraction of the tissue is n_T , while the index of refraction of the immersion fluid, which fills the corrugations providing the surface texture of the specimen 34, have an index n_I . The beam is focused at a focus f in the section to be imaged. The wavefront which may be spherical, can be distorted due to an optical path difference ϕ imprinted on the wavefront which converges to the focus F. This path difference is a function of the product of the corrugation height h and the difference between n_T and n_I . The use of the index matching fluid reduces the optical path difference so that the imprint is minimized. The optical path difference ϕ is shown enlarged at 63 in FIG. 8. This optical path difference may also be viewed as the wavefront which is propagating to the focus F. This wavefront may be spherical and part of a sphere as shown at 68 prior to passing through corrugations at the surface of the specimen 34. The optical path distortion after transmission through the tissue surface is approximated by the relation

$$\phi = h (n_T - n_I)$$

where h is the mechanical depth of surface texture. In order to correct for the distortion of the beam wavefront (which may be a spherical wavefront) by virtue of the variation in index of refraction presented by corrugations, it is desirable that the difference in index of the immersion liquid 38 and the average index of refraction of the tissue multiplied by the corrugation height h that is the optical path distance between the hills and valleys of the corrugation), not exceed a quarter wavelength of the laser beam which is used for imaging in the imaging system 36. Thus, the immersion medium is selected for the tissue type which is placed in the tray and substantially corrects for optical distortion due to the surface texture of the specimen.

In operation, the tray and the specimen are prepared by placing the tissue therein, and positioning the tissue. The tray is then placed in the support 12 and the magnet lock in 56 connects the tray to the objective lens. The lid is closed, piercing the membrane or plug covering opening 46, allowing coupling media to flow upwardly from the bag 44 attached to the bottom portion of tray 10. In an alternative embodiment, the tray may be filled with the immersion liquid before closing the lid and flows down into bag 44 upon lid closing. Then, under operation of the user controls 64, the beam is focused at the section and scanned across the section so as to obtain images of that section. A bar code, or other indicia, may be applied to the tray 10, as on its cover or a side wall for identification and tracking of the specimen, which is especially useful when the tray and specimen are archived (stored for later examination or other use).

Variations and modifications in the herein described apparatus and its method of operation, within the scope of the invention, will undoubtedly suggest themselves to those skilled in the art. Accordingly, the foregoing description should be taken as illustrative and not in a limiting sense.

CLAIMS

1. A specimen holder which comprises a container providing a surface on which a tissue specimen is disposed, a window in said container presenting at least part of said surface through which an optical beam propagates for imaging a section of the specimen or a surface of the specimen, a compliant bag attached opposite to the surface on which the specimen is disposed, an immersion medium having an index of refraction matched to the index of refraction of the specimen in said tray encompassing the specimen, and a coupling medium in said bag.
2. The apparatus according to Claim 1 wherein the index of refraction of the coupling medium is the same as the index of refraction of the immersion liquid.
3. The apparatus according to Claim 1 further comprising an imaging system including an objective lens which focuses an optical beam in the section of the specimen to be imaged, the compliant bag being disposed in physically coupled relationship with the lens.
4. The apparatus according to Claim 3 comprising a support in which the holder is disposed, a fixture connecting the support to the objective lens, and means for varying the positional relationship of the support and the holder therein with respect to the objective lens.
5. The apparatus according to Claim 4 wherein said objective lens is fixed and said means for moving said means for said support is operative to move it in directions along an optical axis of the lens and in directions mutually perpendicular to each other and to the optical axis.
6. The apparatus according to Claim 3 further comprising a transparent stabilization plate attached to the bag opposite to the window and means for releasably assembling the plate and the lens.
7. The apparatus according to Claim 1 wherein said container, including said immersion liquid and said bag, is detachable from said objective lens and removable from said support for disposal after imaging of the specimen.

8. The apparatus according to Claim 1 wherein the container has an openable port through which a liquid medium flows either for the container into the bag or from the bag into the container to provide the immersion medium and the coupling medium.

9. An apparatus for imaging excised tissue having a refractive index comprising:
a tray upon which excised tissue is disposed; and
optics directed towards the excised tissue through a portion of said tray in which said tray contains an immersion media having a refractive index matching the refractive index of said excised tissue.

10. The apparatus according to Claim 9 further comprising means disposed between said tray and said optics which presents a medium between said tray and said optics optically coupling said optics to said tray.

11. The apparatus according to Claim 9 further comprising indicia applied to said tray for identification of said excised tissue disposed therein.

12. A system for imaging a tissue specimen comprising:
a holder having a base with a window upon which a tissue specimen is capable of being located;
means for imaging said tissue specimen through said window when said tissue specimen is located on said window; and
a bag optically transparent to said imaging means which is located between said base of said holder and said imaging means and capable of containing a fluid.

13. The system according to Claim 12 wherein fluid represents a first fluid, and said system holder defines a container including said base for retaining a second fluid.

14. The system according to Claim 13 wherein said second fluid is selected to be substantially correct for optical distortion due to the surface texture of the tissue specimen.

15. The system according to Claim 13 wherein said the first and second fluids have indexes of refraction which substantially match.
16. The system according to Claim 12 wherein said imaging means has an objective lens which focuses an illumination beam through window and said bag to the tissue specimen, in which return light to said imaging means represents a section of said tissue specimen.
17. The system according to Claim 16 wherein said bag has a surface adjacent said window of said base and a transparent plate opposite said surface facing said objective lens of said imaging means.
18. The system according to Claim 12 wherein said imaging means has a barrel having an objective lens directed toward the tissue specimen, and said system further comprises means for coupling said bag to said barrel of said imaging means.
19. The system according to Claim 12 wherein said imaging means is a confocal microscope.
20. The system according to Claim 12 wherein said imaging means is operative by one of optical coherence tomography and two-photon microscopy.

AMENDED CLAIMS

[received by the International Bureau on 12 June 2000 (12.06.00);
new claims 21-23 added; remaining claims unchanged (1 page)]

15. The system according to Claim 13 wherein said the first and second fluids have indexes of refraction which substantially match.

16. The system according to Claim 12 wherein said imaging means has an objective lens which focuses an illumination beam through window and said bag to the tissue specimen, in which return light to said imaging means represents a section of said tissue specimen.

17. The system according to Claim 16 wherein said bag has a surface adjacent said window of said base and a transparent plate opposite said surface facing said objective lens of said imaging means.

18. The system according to Claim 12 wherein said imaging means has a barrel having an objective lens directed toward the tissue specimen, and said system further comprises means for coupling said bag to said barrel of said imaging means.

19. The system according to Claim 12 wherein said imaging means is a confocal microscope.

20. The system according to Claim 12 wherein said imaging means is operative by one of optical coherence tomography and two-photon microscopy.

21. The apparatus according to Claim 1 wherein said tissue specimen has at least one surface substantially planar against said tray.

22. The system according to Claim 12 wherein said tissue specimen has at least one surface substantially planar against said tray.

23. A method for imaging excised tissue comprising the steps of:
providing a container having a surface for placement of said tissue specimen;
placing said tissue specimen upon said surface of said container;
locating a bag with an optical coupling fluid adjacent said container; and
imaging said tissue specimen through said container and said optical coupling fluid of said bag.

STATEMENT UNDER ARTICLE 19

U.S. Patent No. 5,870,223, cited in the International Search Report, shows in FIGS. 2A, 2B, 4A, 4B, 5A, 5B, 6A, and 6B, a specimen (12 or 22) floating or suspended in an immersion fluid of a container. Thus, the specimen is not on, or upon, a surface of a container, tray, or holder as described in the claimed invention of the present application.

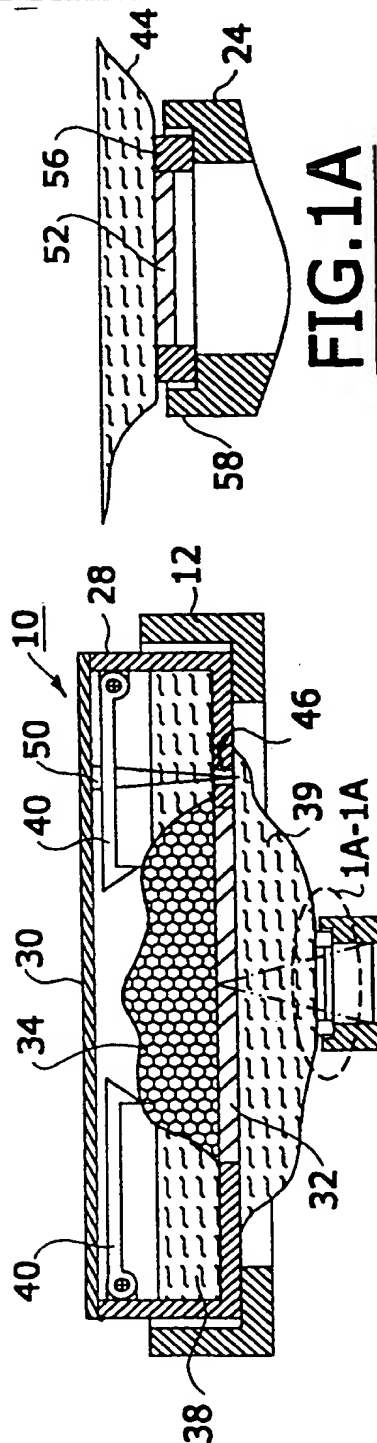


FIG. 1A

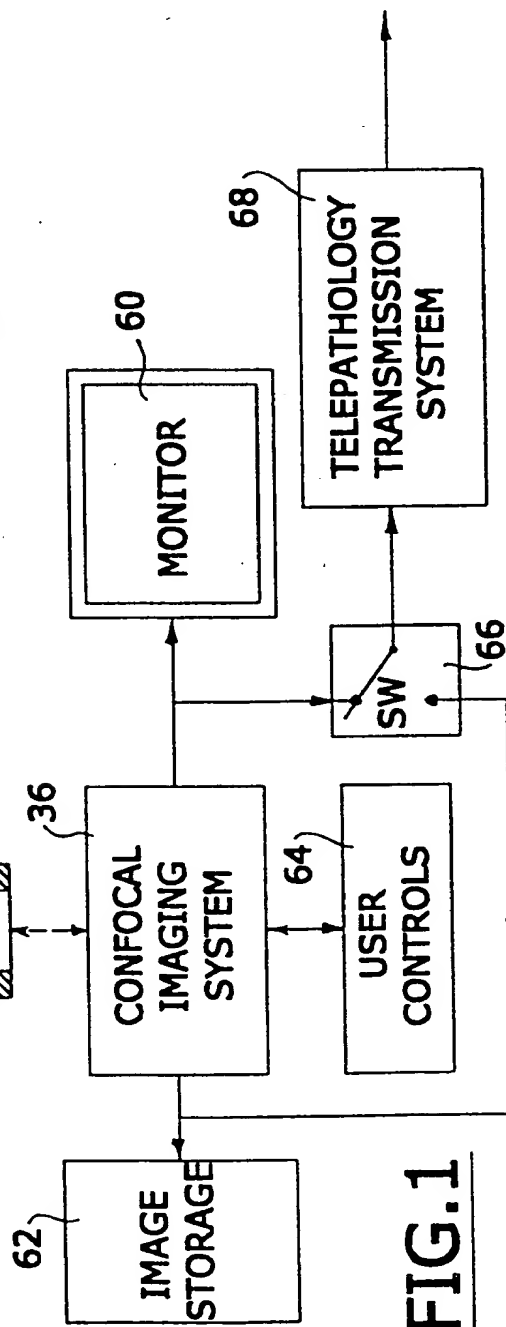
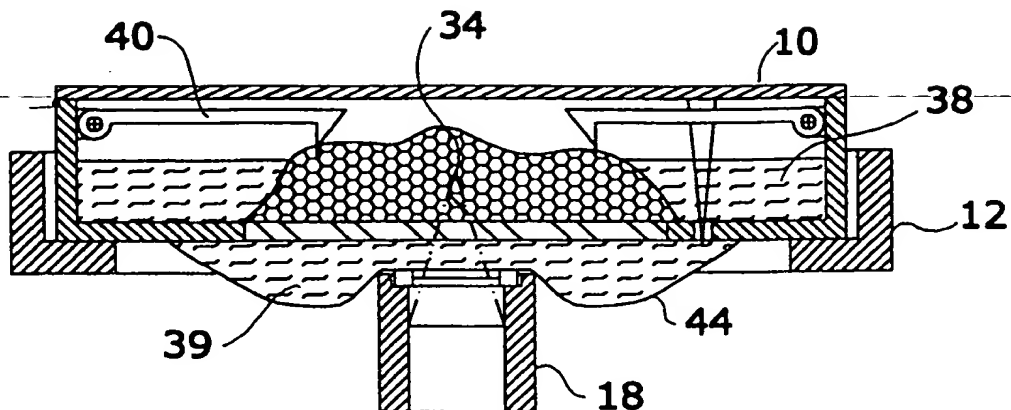
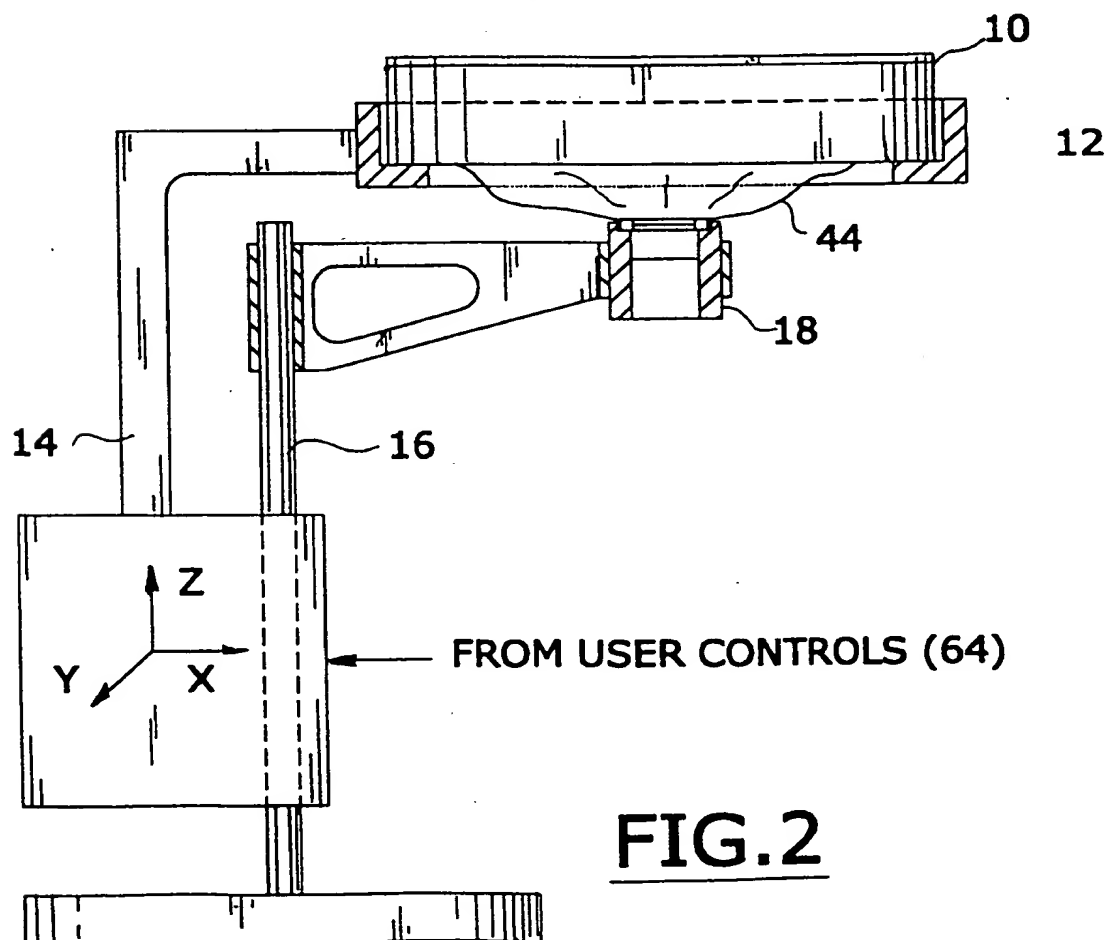


FIG. 1

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**FIG. 1B****FIG. 2**

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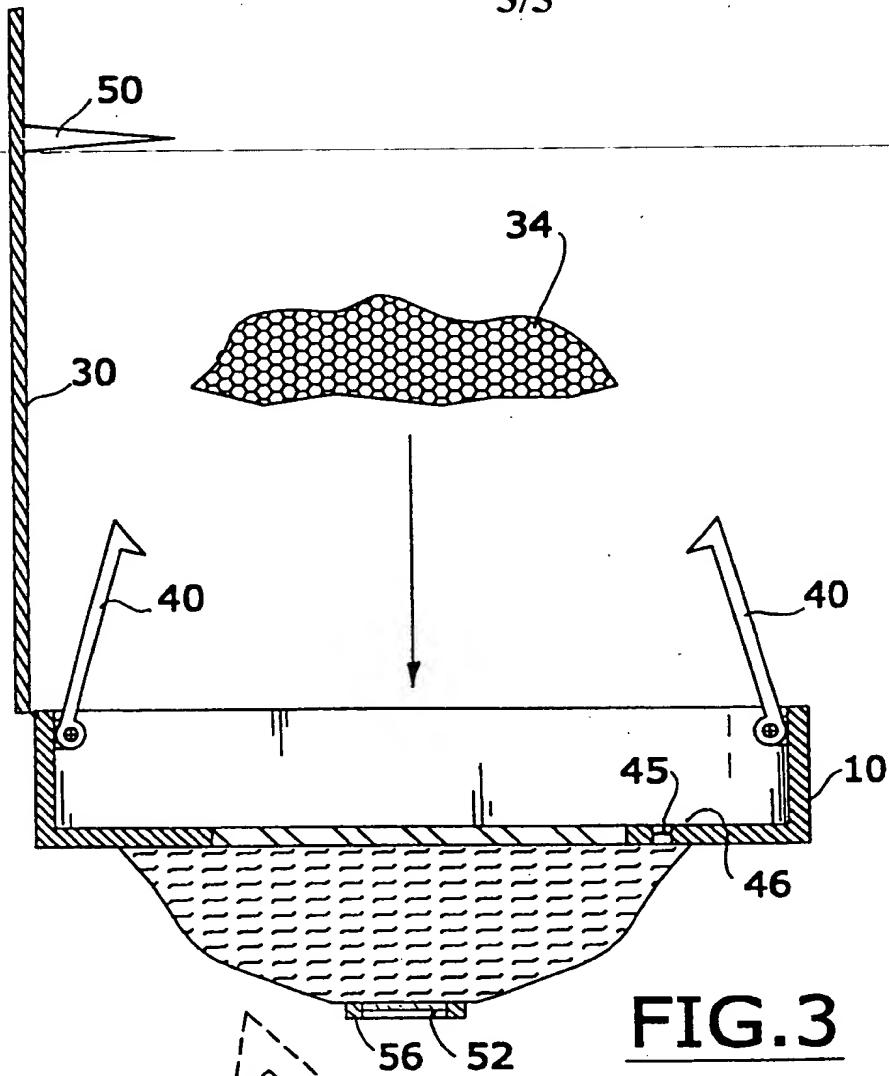


FIG. 3

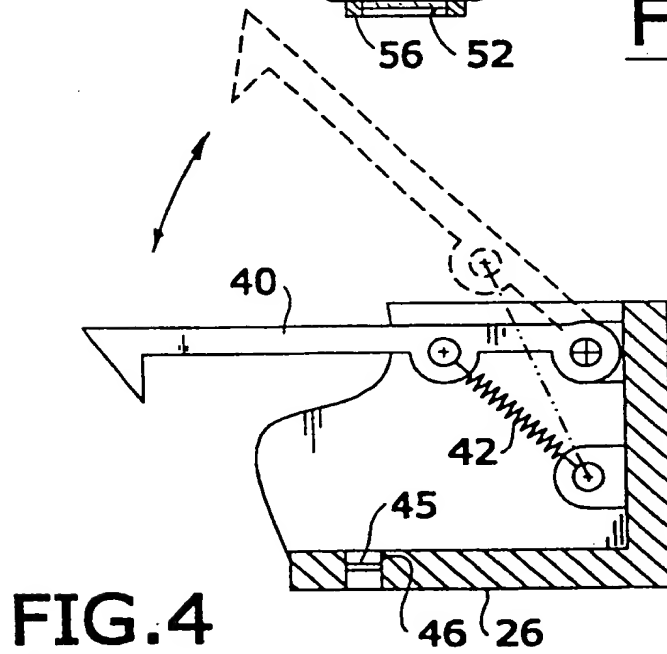


FIG. 4

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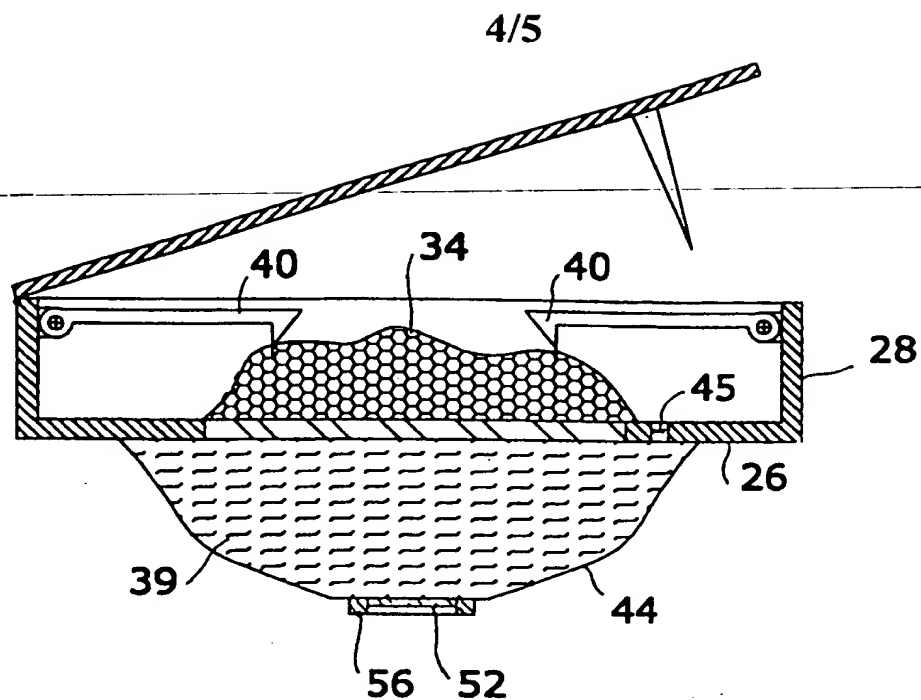


FIG. 5

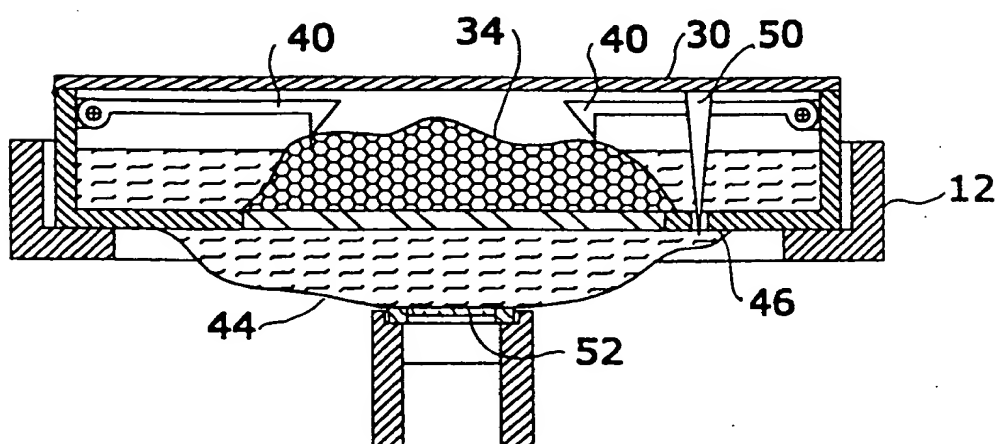
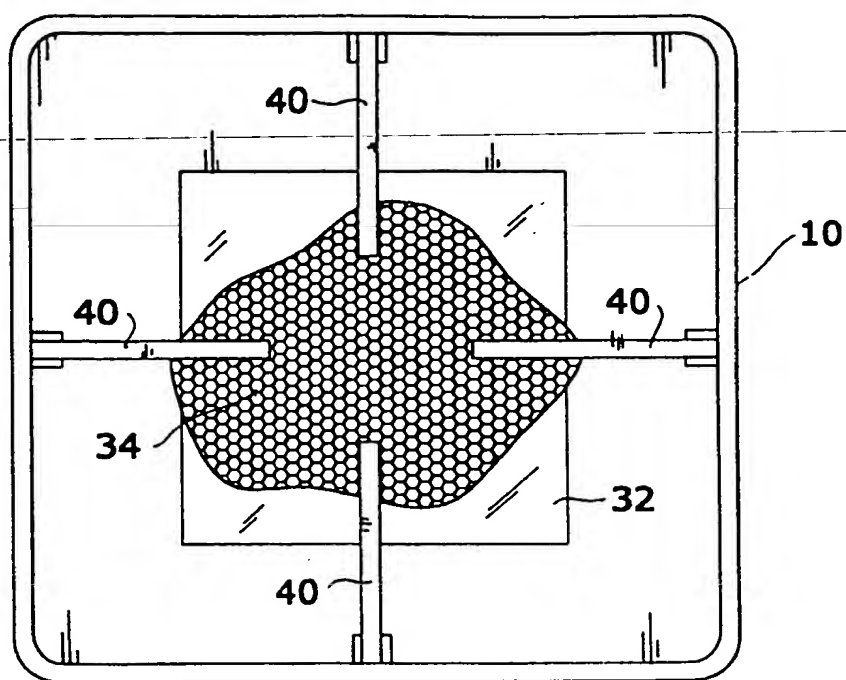
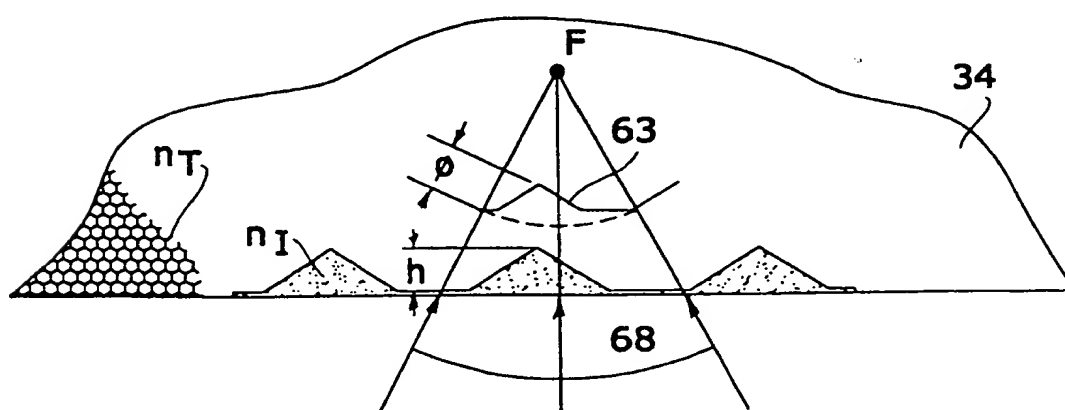


FIG. 6

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FIG. 7FIG. 8

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/04128

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :G 02B 21/34
US CL :359/398

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 359/398

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
359/ 397, 396, 391, 392, 395

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,870,223 A (Tomimatsu) 09 February 1999, (09/02/99) see entire document.	1-20

☐

Further documents are listed in the continuation of Box C.

☐

See patent family annex.

*

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document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search

29 MARCH 2000

Date of mailing of the international search report

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